Membrane Separations: Ultrafiltration. **III/ Immunoaffinity Extraction. Pesticides:** Extraction from Water. **Appendix 1/Essential Guides for Isolation/Purification of Enzymes and Proteins. Essential Guides for Isolation/ Purification of Immunoglobulins. Appendix 2/Essential Guides to Method Development in Affinity Chromatography.**

Further Reading

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Imprint Polymers

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Introduction

Molecular imprinting is now recognized as one of the most rapid and powerful methods for creating tailor-made synthetic receptors with strong, yet selective, affinities for a diverse selection of analytes. The imprinting of small organic compounds, metal ions and peptides is well developed and almost routine, and the imprinting of much larger analytes, such as proteins and cells, has also now been demonstrated. The impressive molecular recognition characteristics of molecularly imprinted materials, allied to their highly robust physical nature, makes them ideally suited for numerous applications in affinity separation. This article will outline the general principles behind molecular imprinting and the generic approaches to the preparation of imprinted materials. Particular emphasis will be placed on their role as affinity materials in separation science.

The Imprinting Principle

Molecular imprinting has been demonstrated in silica and in synthetic organic polymers, but it is organic polymers that have found the most favour and indeed probably have the most to offer to the affinity separation area. The rest of this article will therefore deal exclusively with molecular imprinting in the latter medium.

The technique of molecular imprinting in organic polymers is a polymerization process in which a rigid, and insoluble, macroporous polymer network is formed around an analyte (template) of interest (**Figure 1**). In a typical imprinting experiment the analyte is initially allowed to form, in solution, an assembly with one or more functional monomers, which interact with the analyte via either covalent or non-covalent bonds. Once the assembly has been generated, copolymerization with an excess of cross-linking monomer (usually >50 mol%) is initiated, and the insoluble polymeric product phase separates from solution as the polymerization proceeds. The analyte functions as a template during the

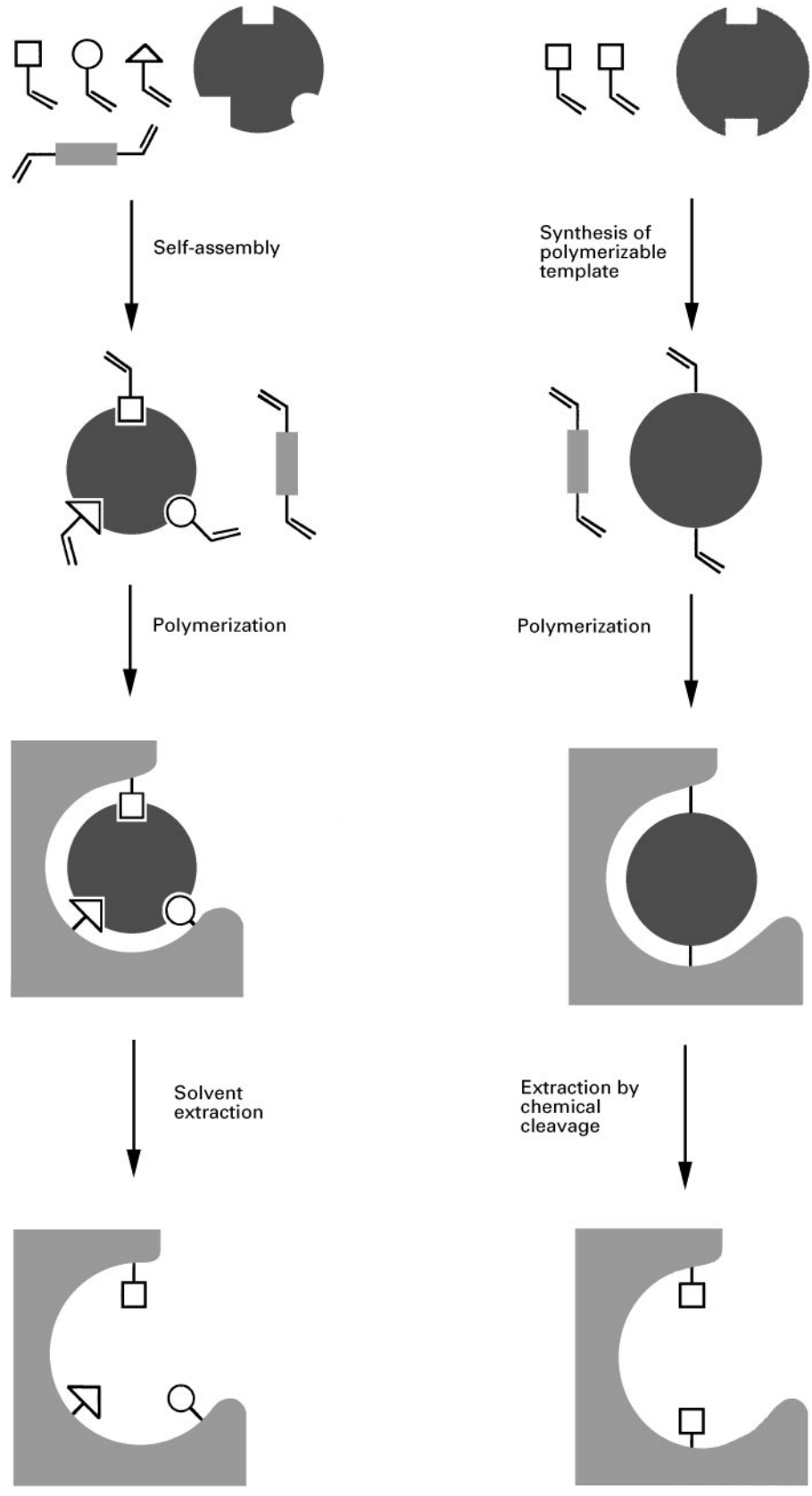

Figure 1 Schematic representation of the molecular imprinting principle. Non-covalent approach (left) and covalent approach (right).

polymerization process, controlling the chemical functionality of the polymer network which forms around it, and since the polymer network is macroporous and the interactions between the analyte and the polymer are quite labile, the analyte can subsequently be extracted from the network via either a simple solvent washing step or by relatively mild chemical treatment. The extraction process reveals binding sites within the polymer network which are complementary to the analyte in terms of their size, shape and functionality, and the polymer can therefore specifically rebind the analyte in these cavities. It is this ability to specifically rebind an analyte which can be taken advantage of in affinity separations.

Numerous analytes have now been successfully imprinted, the majority of which are small, organic compounds, such as drugs, amino acids, sugars and pesticides (**Table 1**). Metal ions and larger organic compounds (e.g. peptides) have also been imprinted. Although the imprinting of much larger analytes, for example proteins and cells, is in principle and in practice somewhat more difficult to achieve, this has now been demonstrated also.

As mentioned already, there are two distinct imprinting approaches that one can follow. The first is the so-called covalent approach (pre-organized approach) in which the interactions between the analyte and the functional monomers in the pre-polymerization assembly are covalent in nature (this classification generally also includes metal-coordinated analytes). Extraction of the analyte from the network requires these covalent bonds to be cleaved, but they are reformed upon subsequent analyte rebinding. In contrast, non-covalent bonds (e.g. hydrogen bonding, ion pairs and π–π interactions) exist between the analyte and the functional monomers in the pre-polymerization assembly in the non-covalent (self-assembly) approach. Rebinding of the analyte to the polymer is also non-covalent in nature.

Table 1 A selection of analytes that have been imprinted

Analytes imprinted	*Examples*
Drugs	Propanolol, diazepam, pentamidine, nicotine
Hormones	Enkephalin
Steroids	Steroidal ketones, cholesterol, testosterone
Amino acids	Various free and derivatized amino acids
Peptides	Various small peptides
Carbohydrates	Various sugar derivatives
Proteins	RNase A, transferrin, haemoglobin
Co-enzymes	Pyridoxal derivative
Nucleotides	NAD^+
Nucleotide bases	9-Ethyladenine
Pesticides	2,4-D, atrazine, triazine
Dyes	Rhodanile blue, Safranine O
Metal ions	Ca^{2+}, Cu^{2+}, Hg^{2+}, Eu^{3+}
Bacteria	*Listeria monocytogenes*

Both imprinting approaches have their own merits and drawbacks, but what can be said in general is that the covalent approach yields binding sites that are better defined. However, it does require chemical derivatization of the analyte prior to polymerization, which is not always easy or practical. The non-covalent method, on the other hand, requires no chemical derivatization step, and is therefore much more general in nature and applicable to a considerably wider range of analytes. Rebinding kinetics are also much more favourable. Indeed, because of its inherent simplicity, the non-covalent approach tends to be the method of choice, although the overall quality of the binding sites tends to be somewhat poorer.

As for the binding sites themselves, the strength and the selectivity of analyte rebinding has been shown in some cases to be on a par with those of natural receptors such as antibodies. This is quite remarkable in itself. In a typical imprinted polymer, however, there is usually a variety of binding sites with different affinities for the analyte, and it is only those sites with the strongest affinities which are comparable to the binding affinities of antibodies. In analogy with antibody terminology, such polymers are usually termed polyclonal to describe their heterogeneous populations of binding sites. There is, needless to say, considerable effort being made to prepare imprinted polymers with homogeneous binding sites, i.e. monoclonal materials.

Besides their impressive molecular recognition properties, molecularly imprinted polymers have several other attractive features. They are exceedingly robust, and can be utilized under conditions which would be disastrous for enzymes or antibodies. They are stable at elevated temperatures and pressures, they are resistant to many chemical environments and can be used in both aqueous and non-aqueous media. Furthermore they are of low cost, have good shelf-lives and can be re-used time and time again without significant detriment to their properties.

In terms of potential applications for imprinted polymers, several avenues are being explored. Imprinted polymers are showing promise as molecular recognition elements in *biomimetic sensors*, as *antibody binding mimics* ('plastic antibodies'), as *catalysts* ('plastic enzymes') and in the *screening of chemical libraries*, but it is in the *affinity separation* area where they are attracting the greatest attention. Indeed, they have already shown their value in chromatography, solid-phase extraction, capillary electrophoresis and membrane separations. Before moving on to consider these applications in greater

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detail, the chemical constitution of molecularly imprinted polymers and general methods for their preparation will be briefly described.

The Preparation of Molecularly Imprinted Polymers

Success in the preparation and application of molecularly imprinted polymers relies upon a good understanding of both the principles and practicalities behind the imprinting process. Although a complete, in-depth guide to the preparation of good quality imprints for all analytes is far beyond the scope of this article, there are some general guidelines which provide a good basis for success. The generalities are covered here. The specific details can be found elsewhere.

Nature of the Analyte

The majority of analytes imprinted to date have been low molecular weight organic compounds of molecular mass 200–300 Da, but with appropriate modification of the imprinting conditions much larger analytes can also be imprinted. Various chemical and physical properties of the analyte are of considerable importance; besides having a suitable chemical handle for interaction with a functional monomer, an analyte must be compatible with the functional monomers and crosslinkers used, it must be soluble in the solvent(s) used for imprinting, and it must be stable and inert under the polymerization conditions employed.

Functional Monomers

Functional monomers are selected based on their ability to bind reversibly, via either covalent or non-covalent bonds, to the analyte. In covalent imprinting approaches, the covalent bonds linking the functional monomers to the analyte need to be reasonably labile to allow removal of the analyte from the polymer matrix under relatively mild conditions. This requirement is somewhat limiting, and only metal-chelates, boronic acid esters, disulfides and Schiff bases have been developed to any great extent. The non-covalent approach is much less restricting in this respect, and numerous vinyl-based monomers have been successfully employed (**Table 2**).

In non-covalent imprinting protocols, the analyte–functional monomer assembly is dynamic in that the functional monomers exist in both the free and the complexed state, and indeed are free to move from one state to another. To push the equilibrium towards assembly formation, it is not unusual to use an excess of functional monomer in the polymerization mixture (typically two-fold or greater). This does have the side effect of increasing the level of non-specific rebinding of the analyte to the polymer, but at the same time it increases the number of good binding sites, so it is a compromise.

Cross-linking Monomers

Copolymerization of the functional monomers with an excess of cross linking monomer (usually >50 mol%) yields an insoluble polymer matrix which phase separates from solution as the polymerization proceeds. High ratios of crosslinking monomers are generally required to give the polymer matrix the rigidity necessary to retain the integrity of the binding sites. Usually analyte rebinding is enhanced considerably as the crosslinking ratio is increased up to 80 or 90 mol%. The improvements in recognition thereafter are much less spectacular. Many different crosslinking monomers have been used, including some which act simultaneously as functional monomers, but the three which have found the most favour are ethyleneglycol dimethacrylate (EGDMA), divinylbenzene (DVB) and trimethylolpropane trimethacrylate (TRIM) (**Table 3**).

Solvents

The solvent, besides acting as the medium in which the polymerization is performed, has an important secondary role as a porogen. It controls the porous structure of the polymer matrix to a large extent, and a good porogen is essential if one wants the porous structure in the polymer to be well developed. Sometimes, however, a good porogenic solvent can be a bad solvent for the analyte, so once again a compromise is sometimes required. Common imprinting solvents include toluene, chloroform and acetonitrile.

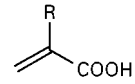
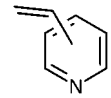
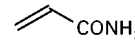
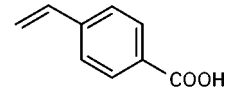
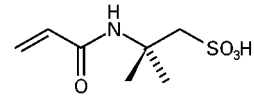
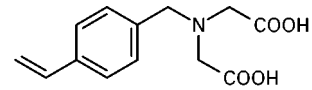
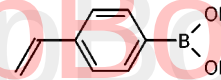
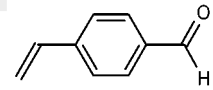
In non-covalent imprinting, there is one further solvent effect which is of great importance. Polar solvents destabilize the analyte–functional monomer assembly and it is therefore better to use non-polar solvents, whenever possible, to maximize the concentration of the assembly in the pre-polymerization mixture. The same argument applies for analyte rebinding. In spite of this, non-covalent imprints have in some cases still shown good recognition properties in aqueous buffers, which are of course highly polar.

One final point of note, which applies to both covalent and non-covalent approaches, is that the best recognition is generally observed when the solvent used for both the polymerization and analyte rebinding is the same.

Initiators and Polymerization Conditions

Classical free radical initiators such as 2,2′-azobisisobutyronitrile (AIBN) are commonly used to

Table 2 A selection of functional monomers commonly used in molecular imprinting

Functional monomer(s)	*Structure*	*Approach*
Acrylic acids	 R = H, CH_3, CF_3 etc.	Non-covalent
Vinylpyridines		Non-covalent
Acrylamide		Non-covalent
Vinylbenzoic acids		Non-covalent
Acrylamido-sulfonic acids		Non-covalent
Vinyl-iminoacetic acids		Metal coordination
Vinylboronic acids (for boronate esters)		Covalent
Vinylbenzaldehydes (for Schiff bases)		Covalent

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initiate the polymerization under either thermal or photochemical conditions. Thermal conditions may be preferred in some cases due to limited analyte solubility at lower temperatures, but photochemical initiation at these lower temperatures has certainly been shown to give better results in non-covalent imprinting.

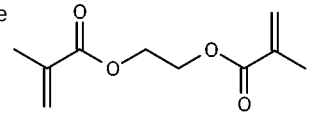
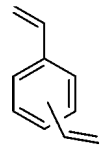
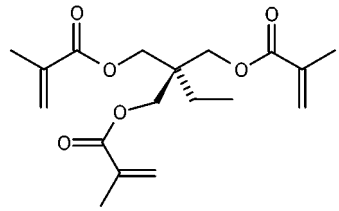
Physical Form of Imprinted Polymers

Molecularly imprinted polymers can be prepared in a variety of forms to suit the final application desired. The most common, and indeed the crudest, method for preparing molecularly imprinted polymers is via solution polymerization followed by mechanical or manual grinding of the monolithic block generated, to give small, molecularly imprinted particles. If required, sizing of the particles through sieving and/or sedimentation can then be performed. Besides being time consuming and wasteful, this method produces particles of irregular shape which are not ideal for chromatographic applications. The grinding process may also destroy a few of the binding sites. Improved polymerization methods which obviate the need for grinding are therefore being investigated.

One seemingly general method which has been developed, and which overcomes the grinding problem completely, involves the suspension polymerization of imprinting mixtures in liquid perfluorocarbon continuous phases. Spherical beads of controlled, regular diameters (down to ca. 5 μm) can be prepared reproducibly by this technique, and are isolated simply by filtration. In the same way, imprinted beads can also be obtained via emulsion, seeded emulsion or precipitation polymerization methodologies.

For chromatographic applications, another solution to the grinding problem is to perform the polymerization directly inside the chromatographic column,

Table 3 Crosslinkers commonly used in molecular imprinting

Cross-linker	*Structure*
Ethyleneglycol dimethacrylate (EGDMA)	
Divinylbenzene (DVB)	 Usually a mixture of isomers
Trimethylolpropane trimethacrylate (TRIM)	

i.e. *in-situ* polymerization. This approach is particularly attractive for capillary electrophoresis applications, where filling of the capillary can often be problematic.

One final format, which is finding increasing interest, involves imprinted membranes. Generally they are composed either of crosslinked polymers which have been prepared in the standard way, or of linear polymers which have been precipitated in the presence of the analyte. They can be either free-standing or supported.

Applications in Separation Technology

As mentioned earlier, the application of imprinted polymers that has been the most extensively explored is separation and isolation. *Chiral separations* have been a major area of investigation, and indeed molecularly imprinted materials have been employed as chiral matrices in several different separation techniques. A characteristic of imprinted chiral separation matrices is the pre-determined migration or elution order of the enantiomers, which depends only on which enantiomer is used as the template molecule. For instance, when the *R*-enantiomer is used as the template, it will be retained more by the polymer than the *S*-enantiomer, and vice versa (**Figure 2**). The discrimination of enantiomers is often very efficient with molecularly imprinted materials. Highly selective, chirally discriminating recognition sites have been prepared using covalent or non-covalent imprinting protocols, and large separation factors between the enantiomers have been recorded.

For analytes containing two chiral centres, all four stereoisomers may be selectively recognized by the imprinted materials. Thus, for a polymer imprinted against the dipeptide Ac-L-Phe-L-Trp-OMe, the LL-form can be selectively distinguished from the DD-, the DL- and the LD-isomers. In systems where more than two chiral centres are involved, such as carbohydrates, these properties of molecularly imprinted materials become even more significant. For example, in a study where polymers were imprinted against a glucose derivative, very high selectivities between the various stereoisomers and anomers were recorded.

Apart from the separation of enantiomers, imprinted polymers are also very useful for the separation of other compounds with closely related structures. An overview of the different separation techniques in which molecularly imprinted polymers have been employed is given below.

Liquid Chromatography

The use of imprinted polymers as stationary phases for HPLC is by far the most studied application. This

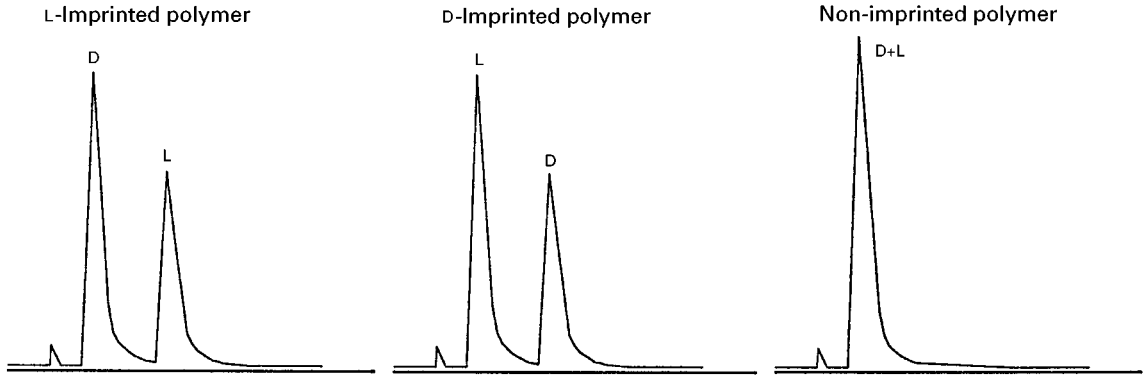


Figure 2 Typical chromatograms of an enantiomeric mixture using a polymer imprinted with the L-enantiomer, a polymer imprinted with the D-enantiomer and a non-imprinted polymer as column packing material.

is partly for historical reasons, because liquid chromatography is a convenient method for assessing the quality of an imprint, particularly during the optimization of an imprinting protocol.

Most research has concentrated on chiral resolution, and molecularly imprinted chiral stationary phases have been prepared for a wide range of compounds. Many of the early investigations employed amino acid derivatives as model substances. In recent years, however, a great deal of emphasis has also been put on the chiral discrimination of drug compounds. Several studies involving the separation of physiologically active compounds, e.g. naproxen (a non-steroidal anti-inflammatory drug), ephedrine (an adrenergic agent) and timolol (a β-adrenergic antagonist) have been described. Typically, separation factors of between 1.5 and 5 are obtained with imprinted polymers, which is relatively high when compared with other chiral stationary phases. In consequence, excellent separations should be possible to achieve in theory, but in practice several factors often lead to rather modest results, especially in terms of resolution. The heterogeneity in the binding site affinities and accessibilities in non-covalently imprinted polymers often leads to band broadening and peak tailing, and thus to a poor column efficiency. Even for non-retained compounds, low plate numbers (2000–5000 m^{-1}) are usually obtained. One factor which has a deleterious effect on the separation is the unfavourable shape and size distribution of particles, which leads to poor flow characteristics and low functional capacities. A good strategy to improve the performance of imprinted stationary phases should therefore take into account the following aspects:

- *Optimization of particle size and shape*. This can be achieved by using suspension polymerization procedures for instance, which can generate uniformly sized spherical beads of controlled dimension.
- *Optimization of the column packing*.
- *Optimization of the mobile phase*. In many cases, the addition of competitors can improve peak shapes, and carefully designed gradient elution protocols can minimize tailing, especially of the more retained peak.
- *Increasing the capacity of the imprinted stationary phase*. This can be realized by optimizing the polymer recipe. It has been shown that substituting trimethylolpropane trimethacrylate for ethyleneglycol dimethacrylate as the crosslinker leads to higher load capacities, since a lower degree of crosslinking is necessary and more functional monomer can be accommodated in the polymer, i.e. the number of theoretical binding sites is increased.

By these means, improved separation and resolution can already be expected. However, the most important issue is certainly the binding site heterogeneity, which is undesirable and has to be addressed. In order to obtain a more homogeneous population of binding sites in an imprinted polymer, the prepolymerization complex between the template and the functional monomers has to be stabilized. Certainly, covalent bonds should give the best results in this respect, but even stronger or multiple noncovalent interactions between monomer and template will afford a more stable complex. For example, acrylamide or trifluoromethylacrylic acid can in some cases be substituted for methacrylic acid, resulting in a considerably improved separation which can be attributed to the stronger noncovalent bonds formed by these monomers as compared to methacrylic acid.

Thin Layer Chromatography

Finely ground imprinted polymer coated on to an inert support has been suggested for use in chiral TLC. Although only a limited amount of work has been done in this area, it has been shown that the racemates of a number of amino acids can be resolved. Problems were encountered due to band broadening, which led to the formation of zones rather than small spots or thin bands. This in turn led to band overlap and poor resolution, and measurements of R_f values were also made more difficult. However, this method may nevertheless be attractive for the determination of the enantiomeric purity of compounds such as a chiral drugs, owing to its simplicity, its speed and the possibility of running multiple parallel samples. Optimization of particle shape, size and porosity, similarly HPLC, will probably result in considerably improved shape of the bands.

Capillary Electrophoresis

The feasibility of using imprinted polymers as selective matrices for affinity capillary electrophoresis and capillary electrochromatography has been demonstrated. Owing to the difficulty in packing ground polymer particles or polymer beads into microbore capillaries, an *in-situ* polymerization seems better suited for this application. Imprinted capillaries have been prepared by *in-situ* synthesis of a macroporous polymer monolith within the capillary, which can be covalently attached to the capillary wall. Ideally, the polymerization is carried out in such a way that

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the capillary is not completely filled with polymer and an axial flow-pore is obtained, which allows the solvent to be exchanged easily. Entrapping imprinted polymer particles in a polyacrylamide gel formed *in-situ* in the capillary has been suggested as an alternative way of preparing imprinted capillaries. However, this approach seems to be somewhat less practical since the solvent cannot be exchanged easily and because the lifetime of such capillaries may be rather short due to problems with air bubble formation during operation.

Enantioselective imprinted columns for capillary electrochromatography could be very useful, especially because considerably higher efficiencies can be obtained ($>100\,000$ plates m^{-1}) than with HPLC columns. Chiral separations of drugs such as the β-adrenergic antagonist propranolol have been achieved within 2 min, and an enantiomeric mixture containing as little as 1% *S*-enantiomer could be resolved. Since imprinted capillaries can be prepared quickly and easily, and are normally very stable in use over a period of several months, this represents a highly promising development for analytical chiral separations.

Membrane-based Separation

Chromatographic separation techniques are well established and widely used, however they do have some limitations, especially in the scale-up of separation processes. For larger-scale separations, they are therefore often replaced by membrane-based techniques, since membranes can be used in continuous mode unlike the batch-wise operation in chromatography.

Polymeric membranes can be made specific for certain target molecules by molecular imprinting. Imprinted membranes have been prepared in different ways; they can be cast directly as a thin layer on a flat surface or between two surfaces, and may or may not contain a stabilizing matrix. Alternatively they can be prepared by a phase inversion precipitation technique. Although imprinted membranes have great potential for applications in separation, especially chiral separation (enantiomeric polishing), they have until now merely been used in model studies and as recognition elements in biomimetic sensors. As an example, molecularly imprinted polymer membranes have been shown to be capable of distinguishing between enantiomers or otherwise closely related molecules. Usually, such membranes facilitate the diffusion of the compound which was imprinted relative to other closely related molecules. Thus, a membrane imprinted with 9-ethyladenine showed faster transport of adenosine than of guanosine. In other applications, selective retention by the membrane of the compound which was imprinted has been observed. For example, chiral discrimination was possible for D,L-phenylalanine, with the passage of the imprinted enantiomer being retarded.

Solid-phase Extraction

Owing to their ability to bind antigens specifically, antibodies have been used in immunoaffinity chromatography and immunoextraction protocols specifically to enrich an analyte prior to its quantification in, for example, medical, food and environmental analysis. Furthermore, it has been demonstrated that the natural receptors can be successfully replaced by imprinted polymers. The use of imprinted polymers for sample concentration and clean-up by solid-phase extraction is attractive due to their high specificity and stability, and also their compatibility with both aqueous and organic solvents. Often the work-up of samples in routine analysis involves a solvent extraction step or a solid-phase extraction step with a more general adsorbent, e.g. an ion exchange or hydrophobic resin. This could be replaced by solid-phase extraction with an imprinted polymer. The advantages are an increased selectivity of the extraction step, and a reduced solvent consumption.

The applicability of this method for analysis has been demonstrated on a number of model compounds such as drugs and herbicides, which can be selectively extracted even from complex samples like beef liver extract, blood serum, urine and bile. For example, the analgesic drug sameridine could be extracted from blood plasma at a concentration of 20 nmol L^{-1}, and subsequently quantified by GC. In this way, much cleaner chromatograms were obtained as compared to the standard liquid–liquid extraction method (**Figure 3**), since fewer contaminants were co-extracted with sameridine by the imprinted polymer-based method.

In analytical applications, problems may be encountered due to small amounts of template remaining in the polymer even after very thorough solvent extraction. This may falsify the results of the analyte quantification following the solid-phase extraction step if traces of the template are released into the sample. A possible solution to this problem is to use, as the template, a molecule with a structure very closely related to the target analyte, rather than the analyte itself. In such a case, the polymer may still bind the target analyte specifically, whereas traces of template liberated during the extraction procedure can be separated from the target analyte upon sub-

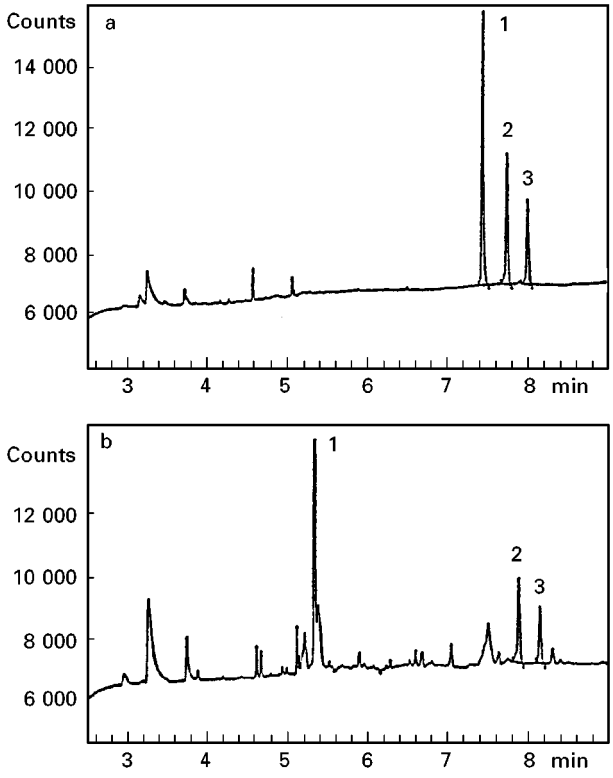

Figure 3 GC traces of human plasma samples spiked with sameridine and an internal standard, and subjected to (a) solid-phase extraction with an imprinted polymer, and (b) standard liquid–liquid extraction. The peaks are the template molecule (1) (a close structural analogue of sameridine), the analyte sameridine (2) and the internal standard (3). (Adapted with permission from *Chromatographia* (1997) 46, 57).

sequent analysis. This approach was demonstrated very nicely for the sameridine case described above, where a close structural analogue of sameridine was imprinted. The polymer displayed a high affinity for sameridine as well as for the analogue, but the two compounds could be readily separated by GC and the sameridine quantified.

Apart from analytical applications, imprinted polymers may also be used for preparative separations, e.g. for product recovery during chemical and enzymatic syntheses, or from fermentation broths or production waste streams. However, for the time being at least, the low binding capacity of imprinted polymers might limit these applications.

It should also be mentioned here that imprinted polymer particles or beads can be made magnetic, which can be advantageous in both analytical and preparative applications since it enables easy removal of the polymer from the extracted medium.

Conclusions

In summary, molecularly imprinted polymers have much to offer to the area of affinity separation. Their highly attractive physico-chemical properties allied to their impressive molecular recognition properties make them particularly well suited for application in a number of important areas, including chromatography, solid-phase extraction, capillary electrophoresis and membrane separations. The period of hitherto unknown expansion, which the molecular imprinting field is currently enjoying, bodes well for the future, and molecularly imprinted polymers will surely play an ever increasing part in affinity separation as the molecular imprinting field matures further.

See also: **II/Extraction:** Solid-Phase Extractions. **III/Chiral Separations:** Molecular Imprints as Stationary phases; Thin-Layer (Planar) Chromatography.

Further Reading

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Molecular Imprint Polymers

See **II/AFFINITY SEPARATON/Imprint Polymers**